Cost-Effectiveness Analysis Based on the Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesion Triage Study (ALTS)

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Background: **The ALTS (atypical squamous cells of undetermined significance [ASCUS] and low-grade squamous intraepithelial lesion [LSIL] Triage Study) suggests that, for women diagnosed with ASCUS, human papillomavirus (HPV) DNA testing followed by referral to colposcopy of only those women with oncogenic HPV (i.e., HPV DNA testing) is as effective at detecting cervical intraepithelial neoplasia (CIN) 3 or cancer (CIN3+) as referring all women with ASCUS for immediate colposcopy. We conducted a cost-effectiveness analysis of the ALTS trial to determine whether HPV DNA testing is a cost-effective alternative to immediate colposcopy or conservative management with up to three cytology examinations.** ***Methods:*** **Data from the ALTS trial were used in conjunction with medical care costs in a short-term decision model. The model compared the incremental costs per case of CIN3+ detected as measured by the incremental cost-effectiveness ratio (ICER) for the following management strategies for women with ASCUS: immediate colposcopy, HPV DNA testing, and conservative management with up to three cytology examinations.** ***Results:*** **The least costly and least sensitive strategy was conservative management with one repeat cytology examination using a threshold of high-grade squamous intraepithelial lesion (HSIL) for referral to colposcopy. Compared with this strategy, triage to colposcopy based on a positive HPV DNA test result had an ICER of $3517 per case of CIN3+ detected. Immediate colposcopy and conservative management with up to three repeat cytology visits detected fewer cases of CIN3+ and were more costly than HPV DNA testing. Immediate colposcopy became cost-effective at $20 370 compared with HPV DNA testing only if colposcopy and biopsy were assumed to be 100% sensitive.** ***Conclusions:*** **HPV DNA testing is an economically viable strategy for triage of ASCUS cytology. The less than perfect sensitivity of colposcopy and biopsy needs to be accounted for in future clinical guidelines and policy analyses. [J Natl Cancer Inst 2006;98:92–100]**

Of the 55 million Pap smears performed each year in the United States, approximately 5% are diagnosed as atypical squamous cells of undetermined significance (ASCUS) *(1)*. ASCUS is the most common abnormal cytology on a Pap test, and a substantial proportion (approximately 39%) of high-grade disease—defined as cervical intraepithelial neoplasia (CIN) grade 2 (CIN2) or CIN3—or cancer occurs among women presenting with this equivocal interpretation *(2)*. However, for the predictive value of the cytology result, only approximately 10% of women with ASCUS have underlying precancer (i.e., CIN3) or cancer *(1)*. Therefore, the optimal strategy for ASCUS triage would be to identify those women with high-grade disease who require follow-up and treatment while limiting the number of women who receive unnecessary procedures.

The ASCUS and LSIL Triage Study (ALTS) is a National Cancer Institute (NCI)–sponsored multicenter randomized trial that was designed to evaluate three management strategies for detection of CIN3 or cancer (collectively referred to as CIN3+) in a US population of women referred for follow-up of ASCUS or LSIL cytology *(1,3–5)*. These strategies include 1) immediate colposcopy; 2) human papillomavirus (HPV) DNA testing with referral to colposcopy of those with oncogenic HPV; and 3) conservative management—i.e., repeat cytology examinations—with referral to colposcopy for women with high-grade squamous intraepithelial lesions (HSIL) or worse. A previous analysis of the ALTS data comparing the performance of the three management strategies in referring women with an initial ASCUS to colposcopy showed that repeat cytology examinations at an ASCUS threshold were as sensitive as HPV DNA testing for detecting CIN3+ but would require two follow-up visits *(1)*, suggesting the possibility of higher costs for the same level of disease detection.

Increasingly, national guidelines include the use of HPV DNA testing to refer only those women with ASCUS who also test positive for oncogenic HPV to colposcopy *(6)*. At least two policy analyses *(7,8)* have been conducted to explore the potential cost-effectiveness of such a policy recommendation; however,

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a cost-effectiveness analysis of the ALTS trial based on the primary data has not yet been performed. Here, we used the ALTS trial data and nationally representative medical care cost data to determine the short-term cost-effectiveness of alternative strategies for the management of women with ASCUS.

Methods

ALTS Trial

In the ALTS trial *(1,3–5)*, 3488 women with cytology findings of ASCUS were randomly assigned to immediate colposcopy; to HPV triage using the Hybrid Capture 2 (HC2) test (Digene, Gaithersburg, MD) *(9)*; or to conservative management based on repeat cytology, with referral to colposcopy for women with HSIL or greater (HSIL+). All women received repeat pelvic exams, cytologic analysis (i.e., Pap tests), and HPV DNA testing every 6 months for a total of 2 years. Also, an exit colposcopy was performed at 24 months to capture any missed disease. The ALTS protocol was reviewed and approved by institutional review boards located at the NCI and at each of the four clinical centers. All study participants provided written informed consent. More details of the trial design and results have been published elsewhere *(1,3–5)*.

The study endpoint was the 2-year cumulative diagnosis of CIN3+. Referral to colposcopy in the three study arms was based on the following criteria: in the immediate colposcopy arm, all women were referred to colposcopy regardless of test results; in the HPV triage arm, women who tested positive for oncogenic HPV at enrollment using the HC2 test at a threshold of 1 pg/mL were referred to colposcopy; and in the conservative management arm, only women with a cytology result of HSIL+ on repeat cytology were referred to colposcopy. At colposcopy, suspicious cervical lesions were biopsied, and endocervical curettage was performed at the clinician's discretion. All women with CIN2 or more severe disease (CIN2+) on tissue biopsy or endocervical curettage were offered the option of the loop electrosurgical excision procedure. Following interpretation at the clinical centers, all cytology and histology slides were sent to the Pathology Quality Control group at Johns Hopkins Hospital for further independent review. Medical management of women was based on the clinical center interpretation of the cytology and biopsy data; however, the final diagnosis used in the analysis of each woman was based on the interpretation from the Pathology Quality Control group. Data from the trial for women enrolled for management of LSIL are not considered in this analysis, because HPV detection was judged too common in LSIL to warrant formal cost–utility analysis *(10)*.

Decision Model

We created a decision analytic model using data from the ALTS trial to evaluate the costs and effectiveness of the three alternative strategies for the management of ASCUS (Fig. 1). The outcomes associated with one, two, or three Pap tests using an HSIL threshold are referred to as conservative management with one Pap test (CM 1 [HSIL]), conservative management with two repeat Pap tests at enrollment and 6 months (CM 2 [HSIL]), or conservative management with three repeat Pap tests at enrollment, 6 months, and 12 months (CM 3 [HSIL]).

We conducted this analysis using a payer perspective, in which intermediate clinical outcomes and direct medical costs were modeled over a short period (i.e., the 2 years of the trial). Direct nonmedical costs and patient time costs were not included in the analysis, and given the short period, cost and effectiveness were not discounted to reflect time preferences. The relative performances of the alternative management strategies were expressed as incremental cost-effectiveness ratios (ICERs), which were calculated as the incremental cost divided by the incremental effectiveness of one strategy compared with the next-most-costly strategy.

For the base case analysis, effectiveness was defined as the number of histologic diagnoses of CIN3+ as defined by the Pathology Quality Control group. Strategies that were more costly and less effective than an alternative were considered to be "strongly" dominated (these strategies are referred to as "dominated" in the text); strategies that had higher incremental cost-effectiveness ratios than the next more effective strategy were considered to be "weakly" dominated (these strategies are referred to as "not cost-effective" in the text). We use the term cost-effective to refer to the incremental cost-effectiveness ratio associated with an intermediate outcome (CIN3+) rather than with life expectancy *(11)*.

Model Assumptions

We made the following assumptions for the base case analysis: 1) in the HPV arm, the HPV DNA test required an additional office visit; 2) test positivity in the HPV arm was calculated using HPV test results from the enrollment visit only; 3) test positivity for the conservative management arm was calculated separately for the enrollment visit and for each of the two follow-up visits, conditional on participation and testing negative at previous visits, with HSIL as the threshold for referral to colposcopy; 4) at the first colposcopy visit, a clinical center diagnosis of CIN2+ on biopsy was the positive threshold for referral to treatment and was used to calculate sensitivity for all study arms; 5) after the first colposcopy visit, women were censored from further analysis in terms of cost and effectiveness, although the "true disease state" of such women was based on worst cumulative histologic diagnosis by the Pathology Quality Control group over the entire 2 years of follow-up; 6) women missing test results in each of the study arms were excluded from the base case analysis. In sensitivity analyses, missing results for HPV were recoded as either positive or negative. Because there were few missing results in the immediate colposcopy and conservative management arms, no such recoding was done for these arms.

Effectiveness Data

Primary data from the ALTS trial were used to calculate the probability of events in the model (Table 1) *(1,3–5)*. Based on the worst Pathology Quality Control histologic diagnosis during the 2 years of follow-up, we calculated the proportion of women who had histologies of normal, CIN1, CIN2, and CIN3+ to assign true disease state (prevalence). We then calculated the probability of a positive test result and the probability of having a positive colposcopically directed biopsy result conditional on disease state. A positive colposcopically directed biopsy result was defined as a clinical center diagnosis of histologic CIN2+. The sensitivity of the different triage strategies for detecting a CIN3+ case depended on both a positive triage test result (i.e., HPV test positivity or cytology of HSIL; there was no triage test for immediate colposcopy) and a positive colposcopically directed biopsy result among women with a true disease state of CIN3+.

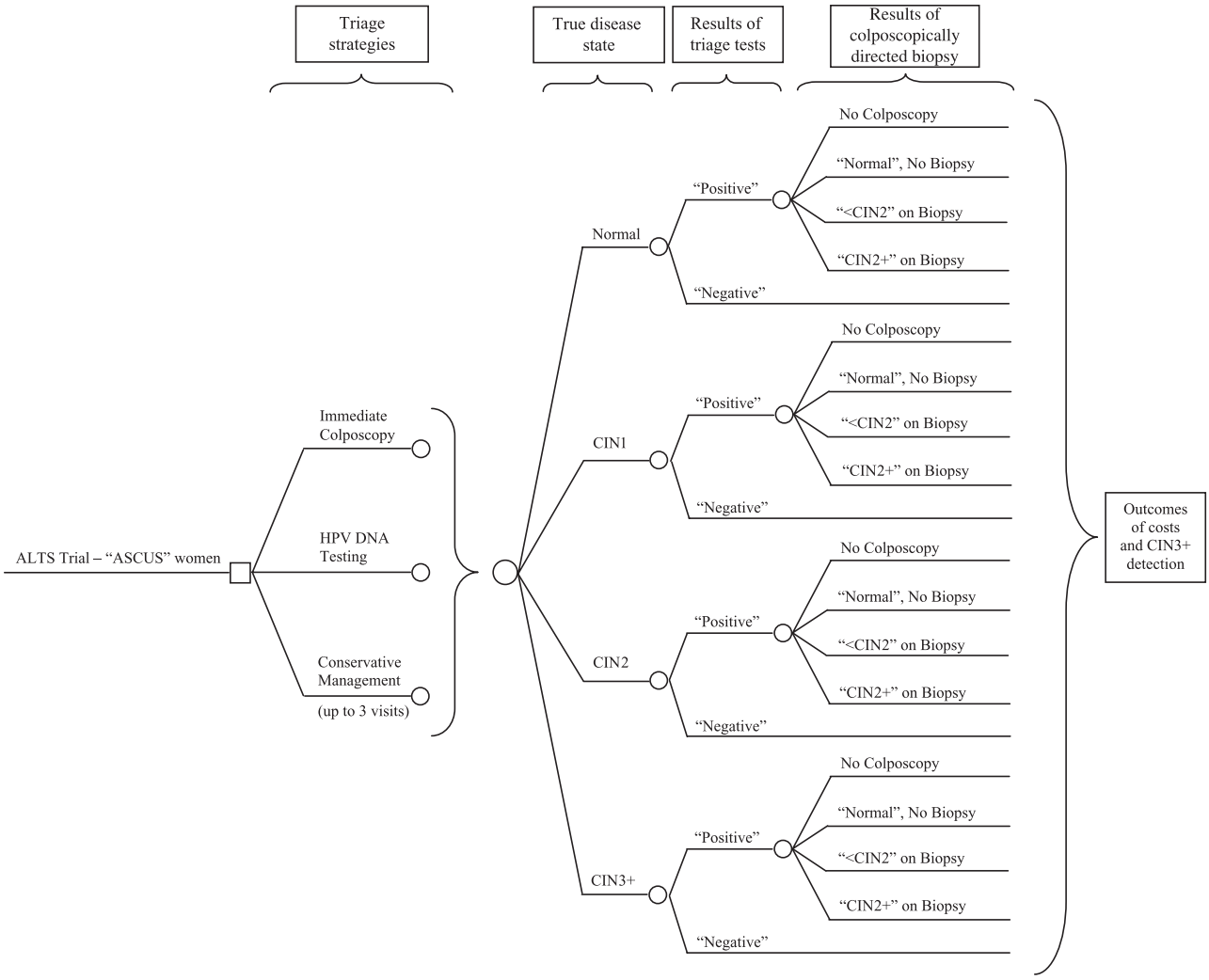

Fig. 1. Decision tree used to determine the cost-effectiveness of three strategies for triage of atypical squamous cells of undetermined significance (ASCUS) cytology. The strategies were: 1) immediate colposcopy; 2) human papillomavirus (HPV) DNA testing; and 3) conservative management, involving a program of up to three cytology visits (at enrollment, 6 months, and 12 months). Triage test results of "positive" and "negative" are relevant only for the HPV and conservative management arms; CIN1 = cervical intraepithelial neoplasia, grade 1; CIN2 = cervical intraepithelial neoplasia, grade 2; CIN2+ = cervical intraepithelial neoplasia, grade 2 or higher; CIN3+ = cervical intraepithelial neoplasia, grade 3 or higher.

Therefore, sensitivity in this analysis refers to the sensitivity of the strategy as a whole rather than just that of the triage test. For the conservative management arm, sensitivity was determined at each visit and was modeled such that overall cumulative sensitivity across all visits matched the data from the trial. We accounted for nonparticipation of women scheduled for repeat visits in the conservative management arm and for nonparticipation of women who were referred to colposcopy in all arms.

Costs

All costs *(12,13)* are shown in Table 2. Only costs associated with the triage strategies and diagnosis were included. These costs, which were restricted to direct medical costs, included costs of repeat screening or triage tests, office visits, and colposcopy with and without biopsy. We accounted for the added laboratory costs associated with physician review of abnormal cytology results in the conservative management arm by using a more conservative threshold of HSIL+ instead of the usual threshold of ASCUS+ necessitating pathologist review. Using this conservative threshold should bias the analysis in favor of lower cost estimates for conservative management. In the base case we used an outcome of cost per CIN3+ detected, but in a sensitivity analysis we included the costs for treatment of CIN (i.e., the loop electrosurgical excision procedure). We used Medicare reimbursement rates to determine costs because these closely approximate societal costs *(11)*. Costs were adjusted for inflation using the medical care component of the consumer price index *(14)*.

Sensitivity Analyses

We performed extensive sensitivity analyses on the base case results. This included stratifying the analysis by age (<30, ≥30 years), using the upper and lower bounds of the 95% confidence intervals for triage test and colposcopy and biopsy sensitivity, and incorporating treatment costs for women with biopsy-confirmed CIN2+. We also conducted an analysis approximating the highest cost estimates for all tests and colposcopy; that is, we assumed that all women referred to colposcopy received both a colposcopy and a biopsy and that the threshold for added costs associated with pathologist review of cytology in the conservative management arm was ASCUS+ (although the threshold for

Table 1. Model variables: base case values by study arm*

	Immediate colposcopy arm (N = 1163)	HPV arm (N = 1161)	Conservative management arm (N = 1164)		
		True disease state (%)†			
No tissue abnormality	66.9	71.1	78.2		
CIN1	16.7	12.8	7.6		
CIN2	8.0	7.4	4.8		
CIN3+	8.4	8.8	9.4		
			Visit 1 (N = 1164)	Visit 2 (N = 1077)	Visit 3 (N = 983)
		Probability of triage test positivity conditional on true disease state (%)‡			
No tissue abnormality	NA	37.9	2.0	0.8	0.1
CIN1	NA	87.6	14.9	6.8	1.5
CIN2	NA	95.3	21.8	23.3	3.1
CIN3+§	NA	94.8 (88.3–98.3)	40.7 (31.4–50.6)	12.5 (5.6–23.2)	21.8 (11.8–35.0)
		Positive colposcopically directed biopsy conditional on true disease state and positive triage test result (%)‖			
No tissue abnormality	1.0	1.0	5.3	0¶	0¶
CIN1	6.7	7.9	30.8	0¶	0¶
CIN2	43.5	45.7	66.7	60.0	0¶
CIN3+§	46.4 (36.2–56.8)	70.3 (59.8–79.5)	90.5 (77.4–97.3)	77.8¶ (40.0–97.2)	75.0 (42.8–94.5)

*Of the 3488 women with atypical cells of undetermined significance (ASCUS) enrolled in the ASCUS and LSIL Triage Study, nine women in the immediate colposcopy arm, eight women in the human papillomavirus (HPV) DNA testing arm, and 20 women in the conservative management arm were excluded from the analysis because of missing data or nonparticipation. In the conservative management arm, women who tested positive (i.e., cytology result of high-grade squamous intraepithelial lesions [HSIL] or worse) and were referred to colposcopy were censored from further analysis. CIN1 = cervical intraepithelial neoplasia, grade 1; CIN2 = cervical intraepithelial neoplasia, grade 2; CIN3+ = cervical intraepithelial neoplasia, grade 3 or higher.

†True disease state determined by worst quality-control histology result across all visits in each study arm.

‡For the HPV arm, the Hybrid Capture 2 test was considered positive if greater than 1 pg/mL; for the conservative management arm, a cytology result of HSIL+ was considered positive.

§Values in parenthesis represent 95% confidence intervals.

‖Colposcopically directed biopsy positivity was defined as having a histologic diagnosis of CIN2 or higher as determined at clinical centers.

¶Estimates were based on fewer than 10 women.

referral to colposcopy remained HSIL+). To approximate the lowest cost estimates, we assumed a reflex HPV test for the HPV arm (i.e., no additional cost associated with another office visit because HPV testing is performed on residual material from the initial liquid cervical sample), no biopsy costs (i.e., only costs for colposcopy were included), and all tests in the conservative management arm used conventional cytology.

The base case analysis compared the cost-effectiveness of the management strategies per the protocol of the ALTS study. We conducted additional analyses to assess the robustness of the base case rankings of the strategies by applying assumptions that are more consistent with current clinical practice. These analyses were as follows: 1) we examined the impact of assuming the same disease prevalence for each arm [using the distribution of disease detected at enrollment in the immediate colposcopy arm *(4)*] instead of the arm-specific prevalence; 2) we repeated the base case analysis using cost per CIN2+ detected via diagnosis at a clinical center (instead of CIN3+ as diagnosed by the Pathology Quality Control group) as the outcome of interest, to reflect the realities of community practice on estimates of cost-effectiveness; and 3) we explored the implications of using ASCUS+ and low-grade SIL (LSIL+) as thresholds for referral to colposcopy on repeat Pap tests in the conservative management arm. For the last analysis, because these cytology thresholds were not used in the actual trial, we assumed that colposcopy and biopsy have perfect sensitivity and specificity for detection of CIN3+. For the last analysis we also made the further assumptions that HPV testing was conducted as a reflex test and that the prevalence of disease was the same for all three arms *(4)* so that the results could be compared with other published cost-effectiveness analyses.

Results

Base Case Results

The least costly strategy was the conservative management strategy of a single repeat cytology with referral to colposcopy

Table 2. Direct medical costs: baseline values and ranges used in sensitivity analyses*

Variable	Base case ($)	Range ($)†
Cytology		
Liquid-based Pap smear	29	14–29
Office visit	55	28–110‡
Physician review (for abnormal results only)	15	10–45
Human papillomavirus test		
Test cost	29	15–45
Office visit	55	28–110‡
Colposcopy (no biopsy) + office visit	174	87–348‡
Colposcopy (with biopsy) + office visit	208	104–416‡
Loop electrosurgical excision procedure	360	190–720‡

*Sources: 2004 Clinical Diagnostic Laboratory Fee Schedule *(12)* and 2004 Physician Fee Schedule *(13)*. Costs are given in U.S. dollars.

†Ranges used in sensitivity analysis for test costs were obtained from a survey of laboratories and experts.

‡Low and high cost estimates were not obtainable; therefore, we conducted analyses varying the cost value from half to twice the value of the base case figure.

Table 3. Base case analysis of costs and outcomes of evaluation of ASCUS*

Strategy	Cost ($)	CIN3+ detected per 10 000	Incremental cost per CIN3+ detected ($)	% Total CIN3+ detected†
CM 1 (HSIL)	100	347	—	36.9
CM 2 (HSIL)	179	401	Not CE‡	42.6
HPV testing	183	583	3517	66.2
Immediate colposcopy	196	390	Dominated§	46.4
CM 3 (HSIL)	252	478	Dominated§	50.8

*ASCUS = atypical squamous cells of undetermined significance; CM 1 = conservative management strategy with one cytology visit; CM 2 = two cytology visits; CM 3 = three cytology visits, all using high-grade squamous intraepithelial lesions (HSIL) as threshold for referral to colposcopy; HPV = human papillomavirus; CIN3+ = cervical intraepithelial neoplasia, grade 3 or cancer; — = baseline strategy. All costs expressed in 2004 U.S. dollars.

†Percentage calculated by dividing number of strategy specific CIN3+ by the total number of CIN3+ Quality Control group diagnoses in each study arm over 2 years.

‡"Not CE" refers to strategies that had higher cost-effectiveness ratios than the next, more effective strategy.

§"Dominated" refers to strategies that were more costly and less effective than an alternative.

using an HSIL threshold (CM 1 [HSIL]) (Table 3). Using this strategy, 347 cases of CIN3+ would be detected on average for every 10 000 women referred for follow-up due to an initial cytology result of ASCUS. Conservative management with two repeat cytology visits using a threshold of HSIL (CM 2 [HSIL]) had a higher incremental cost-effectiveness ratio than triage based on a positive HPV DNA test result; therefore, the strategy was not considered cost-effective. The HPV DNA triage strategy was associated with an incremental cost-effectiveness ratio of $3517 per CIN3+ detected compared with the CM 1 [HSIL] strategy. In the HPV DNA triage strategy, for every 10 000 women referred with an initial ASCUS cytology result, another 236 cases of CIN3+ would be detected on average compared with CM 1 [HSIL]. The immediate colposcopy strategy and the conservative management strategy with three repeat cytology visits using a threshold of HSIL (CM 3 [HSIL]) were dominated—that is, each strategy detected fewer CIN3+ cases and had higher costs than triage to colposcopy based on one positive oncogenic HPV test. As a result, only CM 1 [HSIL] and triage to colposcopy based on a positive HPV test would be considered cost-effective. These results are summarized in Fig. 2, which shows strategies on an efficiency frontier. The cost-effectiveness ratio of a strategy is represented by the inverse of the slope of the line between two points along the efficiency curve. Strategies that fall to the right of the curve are dominated because they are more costly and either less effective (i.e., strongly dominated), or less cost-effective (i.e., weakly dominated) than those strategies that fall on the curve.

Sensitivity Analyses

We assessed the robustness of our base case results by performing several sensitivity analyses. Applying the upper and lower bound of the 95% confidence intervals (for sensitivity of the triage tests and colposcopy and biopsy for detection of CIN3+) did not affect the rankings of the strategies or the magnitude of the incremental cost-effectiveness ratio for HPV DNA testing compared with CM 1 [HSIL]. Analyses of women with ASCUS stratified by age (<30 years versus ≥30 years) showed that, although the costs and outcomes varied by age, the same two strategies were cost-effective in each case: CM 1 [HSIL] and triage to colposcopy based on a positive HPV DNA test. The other three strategies were either not as cost-effective or were dominated. The incremental cost-effectiveness ratio for HPV DNA testing was lower for women in the older age group ($2917 versus $3806 per CIN3+ detected), although the absolute number of cases detected per 10 000 women was more than 2.5 times greater for the younger age group (748 versus 269 cases).

In sensitivity analyses of costs, results were similar when we applied a range of costs for screening and diagnosis or included costs related to treatment. CM 1 [HSIL] remained the least costly and least effective strategy for detection of CIN3+ (data not shown). The incremental cost-effectiveness ratio for triage to colposcopy based on a positive HPV test ranged from $887 to $6470 compared with CM 1 [HSIL]. Triage based on a positive HPV DNA test either dominated or was more cost-effective than immediate colposcopy, CM 2 [HSIL], or CM 3 [HSIL] (data not shown).

We also examined the impact of using CIN2+ as read in a community setting (instead of CIN3+ as read by an expert pathology panel) as the outcome to reflect the current community standard for referral to treatment. The rankings of the strategies remained unchanged: HPV triage had an incremental cost-effectiveness ratio of $1456 compared with the least expensive and least effective strategy for detection of CIN3+, CM 1 [HSIL].

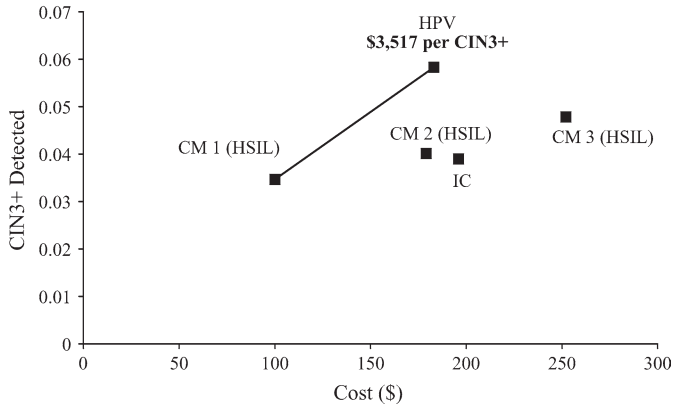

Fig. 2. Base case efficiency frontier depicting the costs and cervical intraepithelial neoplasia, grade 3 or higher (CIN3+) detected with alternative management strategies for triage of atypical squamous cells of undetermined significance (ASCUS) cytology. The cost-effectiveness ratio of a strategy is represented by the inverse of the slope of the line between two points along the efficiency curve. Strategies lying on the efficiency curve dominate those lying to the right of the curve because they are more effective and either cost less (i.e., strongly dominated) or have a more attractive cost-effectiveness ratio (i.e., weakly dominated). CM 1 = conservative management with one cytology visit; CM 2 = conservative management with two cytology visits; CM 3 = conservative management with three cytology visits, all using high-grade squamous intraepithelial lesions (HSIL) as threshold for referral to colposcopy; HPV = human papillomavirus; IC = immediate colposcopy.

Table 4. Sensitivity analysis of costs, CIN3+ detected, and ICER per CIN3+ detected comparing immediate colposcopy, HPV (reflex) testing, and conservative management using HSIL, LSIL, or ASCUS thresholds for referral to colposcopy*

Strategy	Cost ($)	CIN3+ detected per 10 000†	Incremental cost per CIN3+ detected ($)	% Total CIN3+ detected‡
CM 1 (HSIL)	97	208	—	40.8
HPV testing	127	483	1091	94.7
CM 1 (LSIL)	128	335	Dominated§	65.7
CM 2 (HSIL)	176	246	Dominated§	48.2
Immediate colposcopy	182	510	20 370	100.0
CM 1 (ASCUS)	195	439	Dominated§	86.1
CM 2 (LSIL)	207	378	Dominated§	74.1
CM 3 (HSIL)	245	302	Dominated§	59.2
CM 2 (ASCUS)	258	486	Dominated§	95.3
CM 3 (LSIL)	268	416	Dominated§	81.6
CM 3 (ASCUS)	290	496	Dominated§	97.3

*CIN3+ = cervical intraepithelial neoplasia, grade 3 or cancer; ICER = incremental cost-effectiveness ratios; HPV = human papillomavirus; CM 1 = conservative management strategy with one visit; CM 2 = two visits; CM 3 = three visits; HSIL = high-grade squamous intraepithelial lesions; LSIL = low-grade squamous intraepithelial lesions; ASCUS = atypical squamous cells of undetermined significance. All costs are expressed in 2004 U.S. dollars. Prevalence of disease is based on prevalence in the immediate colposcopy arm at enrollment *(4)*. Perfect sensitivity for colposcopy and biopsy and the same prevalence of disease for all three arms were assumed.

†Number of CIN3+ cases detected per 10 000 women.

‡Percentage calculated by dividing number of strategy-specific CIN3+ by the total number of CIN3+ Quality Control group diagnoses in each study arm over 2 years.

§"Dominated" refers to strategies that were more costly and less effective than an alternative.

Immediate colposcopy and CM 2 [HSIL] or CM 3 [HSIL] were dominated or had a higher incremental cost-effectiveness ratio than triage based on HPV testing (data not shown).

We also examined the impact on the relative rankings of using one distribution of disease. When we applied the distribution of disease from the immediate colposcopy arm at enrollment to all three arms, the rank order of the strategies remained unchanged. That is, one repeat visit under conservative management at an HSIL threshold for referral remained the least costly strategy. HPV DNA testing was the next preferred strategy, with an incremental cost-effectiveness ratio of $5373. Other strategies were either dominated by (immediate colposcopy and CM 3 [HSIL]) or had a higher incremental cost-effectiveness ratio than (CM 2 [HSIL]) HPV testing.

For the base case analysis, we assumed that the HPV DNA test required for the HPV arm was conducted at a separate office visit. However, an alternative approach for women whose original screening specimen was collected for liquid cytology would be to perform the cytologic evaluation, and, if the result is ASCUS, to perform reflex HPV testing on material remaining from the original liquid cytology sample. If we assume reflex testing for HPV on liquid cytology samples, the costs of the follow-up office visit and separate sample collection were avoided and the cost of the HPV strategy was reduced, but the effectiveness remained the same, reducing the incremental cost-effectiveness ratio to $1188 per CIN3+ detected compared with the base case value of $3517. Assuming an HPV reflex testing strategy, in the age-stratified analyses the incremental cost-effectiveness ratios changed from $3806 to $1701 for women under the age of 30 years and from $2917 for women aged 30 years or older to HPV reflex testing dominating all other strategies. For the analysis in which we used CIN2+ (as read by clinical center pathologists) rather than CIN3+ (as read by Pathology Quality Control) as the outcome, the incremental cost-effectiveness ratio changed from $1456 to $492, and for the analysis in which we used the distribution of disease based on the immediate colposcopy arm and assumed perfect colposcopy and biopsy sensitivity, the incremental cost-effectiveness ratio changed from $5373 to $1755.

To estimate the incremental cost-effectiveness ratio associated with ASCUS+ or LSIL+ as the threshold for referral to colposcopy in a conservative management strategy, we used the probabilities of triage test positivity from the ALTS data. However, because these thresholds were not used in the trial, we did not have trial-based data on the performance of colposcopically directed biopsy and assumed that both colposcopy and biopsy were 100% sensitive (Table 4). Also, to allow for comparisons with the published literature, we assumed that HPV DNA testing was conducted as a reflex test instead of at a separate office visit and applied the distribution of disease at enrollment from the immediate colposcopy arm to all three arms. CM 1 [HSIL] remained the least costly strategy. HPV triage was the next most cost-effective strategy, with an incremental cost-effectiveness ratio of $1091. HPV triage dominated CM 1 with referral to colposcopy using an LSIL threshold or CM 2 [HSIL]. The next preferred strategy was immediate colposcopy, with an incremental cost-effectiveness ratio of $20 370 compared with triage based on an HPV DNA test. As shown in Table 4 and Figure 3, immediate colposcopy dominated CM 1 with referral to colposcopy using an ASCUS threshold, CM 2 with referral to colposcopy using either an ASCUS or LSIL threshold, or CM 3 with referral to colposcopy using an ASCUS, LSIL, or HSIL threshold. Fig. 3 shows these results in an efficiency frontier.

Discussion

Our results confirm that, for women with ASCUS cytology, HPV DNA triage is an attractive option. Triage based on a positive HPV DNA test detected more CIN3+ cases and was less costly than immediate colposcopy or conservative management with up to three repeat cytology visits with HSIL+ as the threshold for referral to colposcopy (CM 3 [HSIL]). It was also associated with an incremental cost-effectiveness ratio of $3517 compared with one repeat cytology at an HSIL+ threshold for referral (CM 1 [HSIL]). This conclusion was robust over a range of assumptions that included accounting for costs of treatment and using CIN2+ as an outcome, the commonly used threshold in

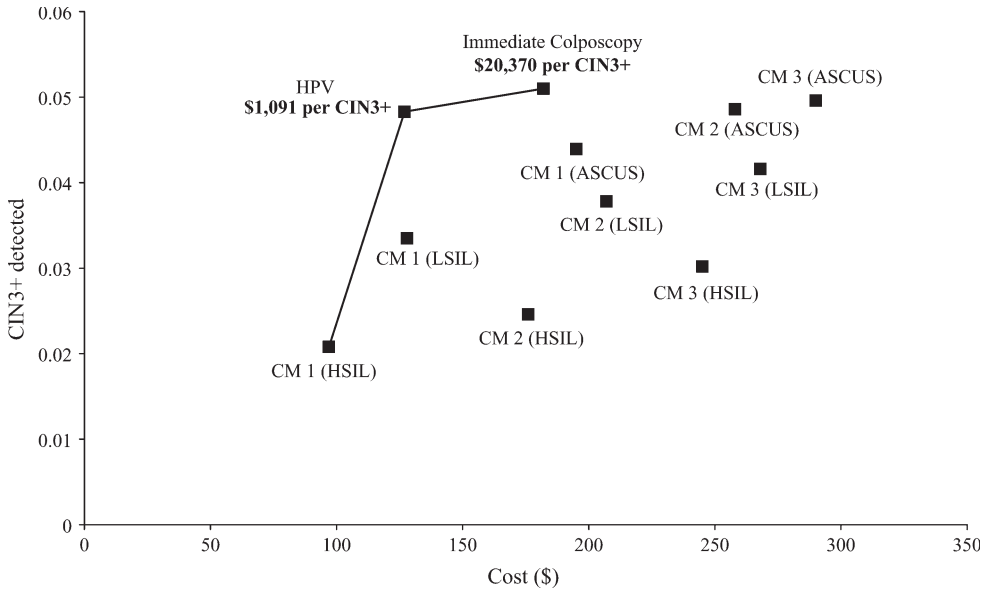

Fig. 3. Sensitivity analysis efficiency frontier depicting costs and cervical intraepithelial neoplasia, grade 3 or higher (CIN3+) detected with immediate colposcopy, human papillomavirus (HPV) testing, and conservative management using thresholds of high-grade squamous intraepithelial lesions (HSIL), low-grade squamous intraepithelial lesions (LSIL), or atypical squamous cells of undetermined significance (ASCUS) for referral to colposcopy, assuming perfect sensitivity for colposcopy and biopsy. CM = conservative management.

the community setting for treatment, rather than a research endpoint of CIN3+. When assuming either high or low costs compared with those for the base case, or if HPV testing was assumed to be obtained as a reflex test instead of a separate office visit, HPV DNA triage was less expensive and more effective at detecting CIN3+ than all other strategies examined for the initial analysis, with the exception of the CM 1 [HSIL] threshold. This strategy was less expensive but detected the fewest cases of CIN3+.

Our sensitivity analysis showed that the accuracy of one colposcopy-directed biopsy visit for detection of high-grade disease is one of the key variables driving the conclusions of this economic analysis. A comparison of the detection rates in each arm showed that 46.4% of the total CIN3+ (diagnosed using a quality-control panel) was detected in the immediate colposcopy arm compared with 66.2% in the HPV triage arm. The difference in CIN3+ detection between the immediate colposcopy and HPV arms, which was based on data from only the enrollment visit, suggests that knowledge of HPV and cytology test results play a role in disease detection. In ALTS, immediate colposcopy was performed before clinicians received results from the triage tests; however, they were aware of the test results in the HPV triage arm. Thus, they may have looked more closely for disease if the patient had been referred because of a positive HPV DNA test or abnormal cytology.

When we assumed that colposcopy and biopsy had 100% sensitivity, immediate colposcopy was more effective than reflex HPV testing, as would be expected. These results show that the assumption of 100% sensitivity can result in a different cost-effectiveness ranking of the strategies. This effect underscores the need to account for the imperfection in detecting disease, which is in contrast to what is currently assumed in clinical practice and cost-effectiveness analyses of cervical cancer screening. As we move to less frequent screening in subgroups of women (e.g., repeated negative HPV and cytology results) *(15)*, we must be mindful of the assumption we have made in the past about the performance of colposcopy and explicitly model the detection error in our analyses.

An interesting finding was the impact on the rankings of the ASCUS management strategies of analyzing by age. Among women younger than 30 years, immediate colposcopy was less effective at detecting CIN3+ and more costly than a conservative management strategy based on up to two repeat visits with referral to colposcopy using an HSIL+ cytology threshold. HPV DNA testing was more costly than either strategy but was also more effective in detecting CIN3+. By contrast, among women aged 30 years or more, HPV DNA testing was less expensive than immediate colposcopy or triage to colposcopy based on either two or three repeat cytology tests and more effective in detecting CIN3+. These results indicate that triage to colposcopy based on HPV DNA testing may be more specific in older women, a finding that is not surprising given the lower prevalence of HPV infection in older women *(16)*.

There are several limitations to our study. Our analysis modeled an intermediate outcome (CIN3+) over a short horizon and did not include patient preferences; we were therefore unable to estimate the cost per year of life or quality-adjusted life-year gained. Use of a short time horizon for this analysis may overemphasize the benefits of detecting CIN3+ in the HPV arm compared with the conservative management arm if screening beyond 2 years detects more, previously missed cases. Other analyses *(7,8)* that have been able to extend short-term outcomes to long-term summary measures have relied almost exclusively on secondary data to estimate these measures and have made several assumptions in the absence of primary data. For example, both Kim et al. *(7)* and Maxwell et al. *(8)* assumed colposcopy and biopsy to be 100% sensitive in the absence of actual data on sensitivity. By contrast, our analysis incorporated primary data from the largest randomized trial designed to evaluate ASCUS management strategies. Interestingly, despite different data, study design, and model structure, these analyses support similar conclusions about the attractiveness of HPV DNA testing as a triage strategy for ASCUS. Kim et al. *(7)* compared immediate colposcopy, triage based on HPV reflex testing, and repeat cytology with referral to colposcopy (≥ASCUS threshold). Maxwell et al. *(8)* compared a strategy of reflex HPV DNA testing with a strategy based on one repeat cytology with referral to colposcopy using an ASCUS threshold. When we assumed that colposcopically directed biopsy was 100% sensitive, our results were consistent with those of Kim et al. *(7)*, who reported that immediate colposcopy was more effective than reflex HPV testing, and with

those of Maxwell et al. *(8)*, who reported that conservative management using one cytology was more costly and less effective than HPV reflex testing.

Another limitation that should be considered in evaluating our results is how we defined and modeled disease prevalence. Disease prevalence was based on the determination of disease using an expert pathology panel during 2 years of follow-up. An implicit assumption in our base model is that disease detected during the 2 years of follow-up corresponds to "missed" prevalent disease. For CIN3+, the results from the trial suggest that this is a reasonable assumption *(1)*. However, for CIN1 and 2, the "prevalence" varied among the three arms. Fewer CIN1 and CIN2 cases were detected in the conservative management arm than in the HPV or immediate colposcopy arms, possibly due to a delay in detection by conservative management that allowed for regression of some lesions. To determine whether applying the same prevalence to all three arms would change the rankings of the strategies, we used the enrollment data from the immediate colposcopy arm *(4)*. As discussed, the relative rankings of the strategies did not change, but the incremental cost-effectiveness ratio was higher for HPV DNA testing than in the base case, again suggesting the need to consider how imperfections in the sensitivity of colposcopy and biopsy affect disease definition and how these imperfections, in turn, affect cost-effectiveness analyses.

Another possible limitation is that although using primary data from a randomized trial reduces concerns of bias, some of the ALTS trial conditions do not mirror community practice. For example, patient retention was maximized by use of patient incentives and intensive outreach efforts by study staff that would be difficult to replicate in the community setting. Higher rates of loss to follow-up might reduce the effectiveness (and decrease costs) of strategies such as conservative management with multiple repeat visits. Moreover, the trial used CIN3+ as the measure of effectiveness (as defined by an expert pathology panel) for each arm of the trial. However, the current standard for treatment in the United States is CIN2+ as read in a community setting. To address this difference, we examined whether use of CIN2+ as diagnosed by community pathologists would change the ranking of ASCUS management strategies. We found that the rankings of the strategies did not change. However, the fact that there were fewer CIN2+ cases detected over the 2 years in the conservative management arm than in the HPV and immediate colposcopy arms indicates that traditional cost-effectiveness models that combine CIN2 and CIN3 into one high-grade disease state may be obscuring an important distinction that may have cost implications. More important, this distinction may potentially avoid overtreating women *(17,18)*.

Because the intent of this analysis was to model ASCUS triage strategies and colposcopic detection of disease, we could not examine postcolposcopy management recommendations such as those put forth by the American Society for Colposcopy and Cervical Pathology guidelines *(19)*. However, previous studies *(7,8)* that used a longer period have found results similar to ours. Finally, any decision to adopt HPV triage for women with ASCUS cytology must be balanced against the need to prioritize resources for unscreened or underscreened women.

In conclusion, this cost-effectiveness analysis of the ALTS trial suggests that triage based on HPV DNA testing for women with ASCUS cytology results is an economically viable option. Our analyses highlight that future cervical cancer cost-effectiveness analyses should account for the less than perfect performance of colposcopy and biopsy in the detection of disease.

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Notes

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